PROTOCOL: TriShapeMatch-10
(with ShapeAUSEx-12 Extension Study)
Version: 8.0
Date: 21 August 2012

A prospective, non-randomized, longitudinal study of the clinical outcomes of participants that receive the Stryker Triathlon Total Knee System for Total Knee Arthroplasty implanted using ShapeMatch® Cutting Guides.

With Extension Study:

A follow-up, longitudinal study of the clinical and radiographic outcomes of participants that receive a Triathlon Custom Fit Knee® using Stryker ShapeMatch® Technology:

Sponsor: Stryker Australia Pty Ltd (ABN: 48002 873 850)
8 Herbert Street, St Leonards, NSW 2065
Contact: Tim Barker PhD, Director of Clinical Research
Ph: 02 9467 1000

I have read and agree to follow this protocol and the NHMRC National Statement on Ethical Conduct in Research Involving Humans:

Principal Investigators:

Dr Gavin Clark	_____ Signature	__/__/__ Date
Dr Ton Tran	_____ Signature	__/__/__ Date
Dr Adrian Trivett	_____ Signature	__/__/__ Date
Dr Bob Steele	_____ Signature	__/__/__ Date
Dr Peter McEwen	_____ Signature	__/__/__ Date

TABLE OF CONTENTS

1.0 SUMMARY

This is a prospective, non-randomized, longitudinal study of the clinical outcomes of participants that receive the Stryker Triathlon® Total Knee System for Total Knee Arthroplasty implanted using ShapeMatch® Cutting Guides. Health status and functional outcome measures will be recorded to quantify functional status of subjects before surgery and at each follow-up interval.

There will be 4 sites and 6 investigators for this study. A maximum of 160 cases will be enrolled in the study and it is expected that participants will be recruited over a 6 month period. Total duration of the study is expected to be 1.5 years.

The study consists of two groups:
Group A: Assessment of the intra-operative reproducibility of placement of the ShapeMatch® Cutting Guides onto the distal femur and proximal tibia bone surfaces;

Group B: Assessment of the placement of the ShapeMatch® Cutting Guides intra-operatively combined with an assessment of post-operative patient outcomes compared to pre-operative status and post-operative implant placement.

Pre-operatively, all participants will be required to undergo medical imaging assessment using Magnetic Resonance Imaging (MRI) of the affected lower limb. These images will then be used to manufacture the patient-specific cutting guides for preparation of the bones prior to implantation of the total knee replacement.

For Group A, participants will only undergo intra-operative assessments to determine repeatability of the placement of the cutting guides onto the distal femur and proximal tibia. No post-operative evaluations will be specifically required of participants due to their involvement in this study.

For Group B, participants will be requested to attend visits pre-operatively and post-operatively at 6 weeks, 3 months and 6 months. At these visits will complete assessments relating to quality of life, pain and functional outcome. In addition, participants will have standard knee X-rays taken pre-operatively and post-

operatively. A post-operative CT scan will be obtained for all participants in order to assess implant position and orientation.

All implanted prosthetic components (Stryker Triathlon Primary Total Knee System) used in this study are TGA approved for sale and use in Australia. This study was originally to be undertaken via the Clinical Trial Notification (CTN) Scheme of the Therapeutic Goods Administration (Therapeutic Goods Act, 1989); however the ShapeMatch® Cutting Guides are now also listed on the Australian Register of Therapeutic Goods (ARTG) for sale and use in Australia.

This study will adhere to all relevant requirement and guidelines in relation to the conduct of clinical trials, including the Declaration of Helsinki (Appendix 5) and ICH Good Clinical Practice Guidelines, as implemented in Australia (Appendix 6).

An Extension Study will be undertaken to follow Group B patients who consent to continued follow-up. These patients will be followed out to 5 years post-surgery with follow-up visits at 12 months, 2 years and 5 years in order to collect longer term data on radiographic and patient outcomes.

Visit Windows

Definition – Since it is not always possible for subjects to come in for a study visit on the exact date, most protocols allow a certain time period before or after the calendar date; this is known as the visit window. If a subject is not seen during the visit window, that visit will be regarded as a missed visit. Visit windows are calculated in reference to the baseline date, which is the surgery date (intra-op) for this study.

Patient Evaluation Schedule

Part A: Reproducibility sub-study

EVALUATION	History/ Pre-Op	Intra-Op
Demographics	✓	
Medical History	✓	
MRI	✓	
Surgical Details		✓

Note: No post-op visits required for participants in Part A.

The visit windows for this study are:

- Pre-Op = Within 2 months before the date of surgery

Part B: Functional outcome sub-study

EVALUATION	History/ Pre-Op	Intra-Op	6 week	3 MO	6MO
Demographics	✓				
Medical History	✓				
MRI	✓				
Surgical Details		✓			
International Knee Society Score	✓			✓	✓
KOOS	✓		✓	✓	✓
SF-12 v2	✓		✓	✓	✓
VAS Pain	✓		✓	✓	✓
AP and ML X-rays	✓		✓		
Perth CT Protocol				✓	✓*

The visit windows for this study are:

- Pre-Op = Within 2 months before the date of surgery
- Intra-op = Baseline time point
- 6 Weeks = +/- 2 weeks
- 3 Months = +/- 1 month (+/- 6 weeks for CT only – except WA site)
- 6 Months = +/- 1 month(+/- 6 weeks for *CT WA site Only and X-ray only)

Extension Phase:

EVALUATION	12 month follow-up	2 year follow-up	5 year follow-up
Demographics	✓		
BMI	✓	✓	✓
Medical History Review	✓		
Surgical Details	✓		
Knee Society Score	✓	✓	✓
KOOS	✓	✓	✓
SF-12 v 2	✓	✓	✓
VAS Pain	✓	✓	✓
Forgotten Joint Score	✓	✓	✓
Anteroposterior (A/P) and Lateral Knee Radiographs	✓		✓
Long leg (A/P) weight bearing x-ray	✓		✓
Adverse Events	✓	✓	✓

The visit windows for this study are:

- 12 Months = +/- 3 months
- 2 years = +/- 3 months
- 5 years = +/- 4 months

2.0 INTRODUCTION

Total knee replacement has evolved to a point where implant design combined with instrumentation and surgeon skill results in excellent implant survival. Over 30,000 total knee replacement procedures are performed each year in Australia and are used to treat a range of conditions including osteoarthritis, rheumatoid arthritis, avascular necrosis and secondary arthritis resulting from trauma.

Current surgical techniques make use of generic, re-usable instrumentation, consisting of intra- and/or extra-medullary rods on the femur and tibia to determine alignment in relation to anatomical landmarks, combined with bone resection guides which ultimately determine position and orientation of the definitive implant components.

Traditionally, the goal of total knee replacement has been to position the components such that the post-operative alignment goal is a straight limb, or a mechanical axis of 0° (Insall & Scott, 2001). The mechanical axis is defined by lines joining the centre of the femoral head, centre of the knee joint and the centre of the ankle. Despite the best efforts of the surgeon, the resulting limb alignment varies away from 0° by a small amount (typically ±3° in 80% of cases).

More recently, the use of computer navigation systems has been introduced to surgical practice with the aim of improving the ability to obtain post-operative limb alignment as close as possible to 0° (Chauhan et al, 2004).

Whilst achievement of neutral limb alignment has been considered desirable from an engineering point-of-view – to maximize implant longevity through minimizing the deleterious effects of polyethylene insert wear and particle-induced osteolysis and implant loosening – patient satisfaction of total knee replacement has not always been ideal. Despite surgery being performed technically correct by surgeons, up to 1 in 5 patients express dissatisfaction in the functional result (Bourne et al, 2009). Patient expectations after surgery are also increasing due in part to the adoption of more active lifestyles amongst total knee replacement recipients where return to function can be of primary importance.

The opportunity exists to provide an alternative approach to total knee replacement surgery which may result in improved patient outcomes. One such approach is to determine the optimal placement of components based on the individual anatomy of patients, rather than a generic limb alignment philosophy (Coughlin et al, 2003; Eckhoff et al, 2005). This approach relies on the creation of a pre-arthritic model of the bone and cartilage structures of the knee. A single, 3-D axis of rotation is then determined which takes into account the 3-D shape and orientation of the femoral condyles during the weight-bearing portion of gait. This is in contrast to traditional surgical techniques which set femoral component orientation and position using one or more of the trans-epicondylar axis, posterior-condylar axis and/or the anterior-posterior (or Whiteside's) line. This new axis is then the basis of determining the so-called natural alignment goal for the joint replacement procedure.

A comprehensive three-dimensional description of the anatomy can be obtained by magnetic resonance imaging (MRI) scans obtained pre-operatively. Through a proprietary process, it is possible to pre-operatively develop a model of the arthritic bone and cartilage, adapt that model to take into account degenerative process, and generate a model of the pre-arthritic anatomy (Appendix 1, Fig. 1). The pre-arthritic state then becomes the surgical goal in terms of limb alignment. Custom cutting guides are generated for each individual patient to enable the surgeon to perform the bone resections in such a way that the resultant construct with the total knee replacement components reproduces the pre-disease limb alignment (Fig. 2). Early experience of applying this technique indicates that patient outcomes and function assessed during the early post—operative phase are superior to conventional approaches to total knee replacement (Howell et al, 2008; Spencer et al, 2009). Other potential advantages of this technology include a reduction in blood loss (as no intramedullary rod is used), and a reduction in ligament releases (as the total knee components effectively resurface the knee with restoration of the natural alignment) (Howell et al, 2008).

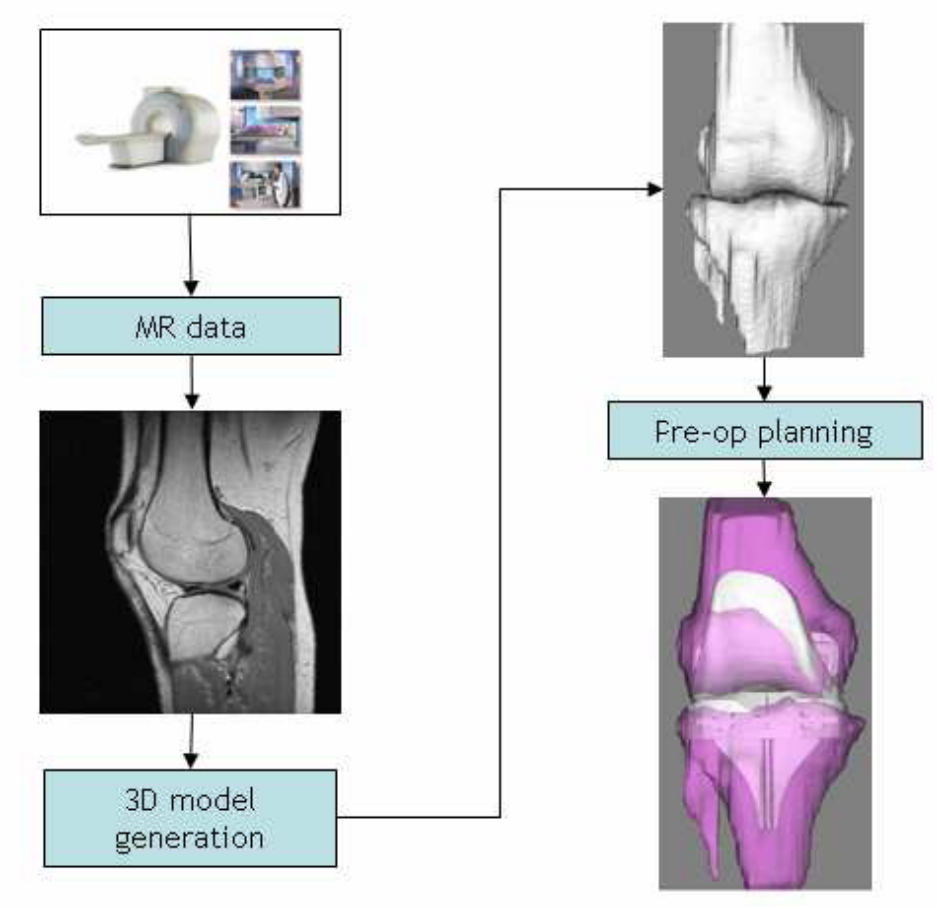

Figure 1: Workflow and data transfer process used for preparation of ShapeMatch® Cutting Guides.

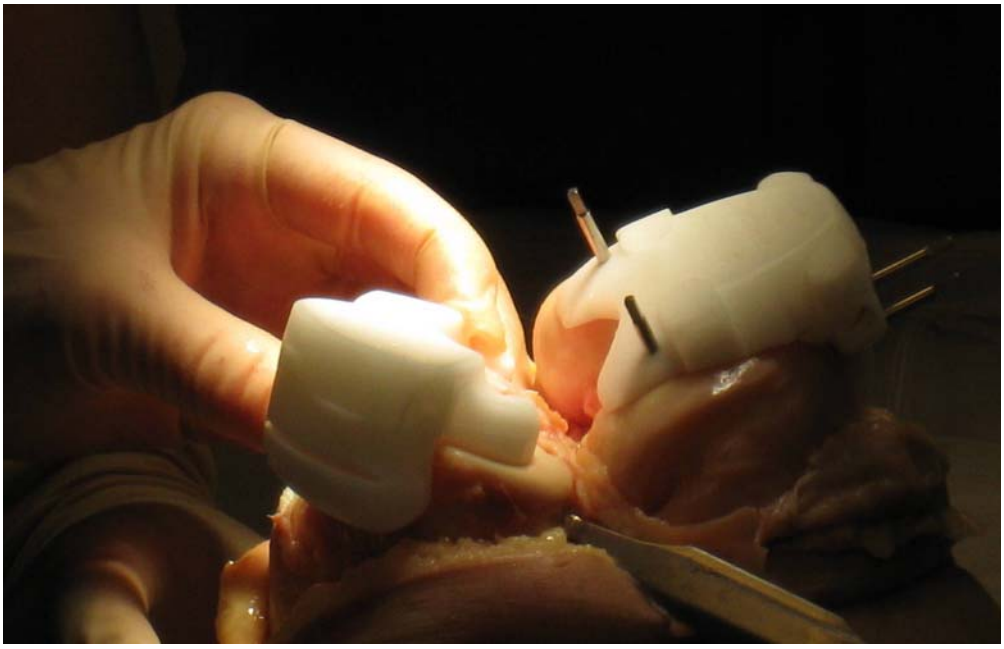

Figure 2: Intra-operative image of ShapeMatch® Cutting Guides positioned on distal femur and proximal tibia. Femoral cutting guide has been pinned in place, ready for bone resection. Tibial cutting guide being positioned prior to pinning.

This protocol outlines a study for the systematic assessment of this new approach to total knee replacement.

This study consists of two distinct parts:
Group A: This sub-study aims to quantify the reproducibility of positioning the cutting guides onto the affected femoral and tibial joint surfaces.

Group B: This sub-study aims to assess certain aspects of the operative procedure, as well as measure parameters relating to quality of life, pain and functional outcome using standard orthopaedic scoring methods.

Following on from Group B, an extension study will be undertaken. This study aims to determine the clinical and radiographic outcomes out to 5 years post surgery, in patients receiving a Triathlon Custom Fit Knee featuring Stryker ShapeMatch

3.0 OBJECTIVES

The primary endpoints of this study are:

1. Repeatability of cutting guide position on the distal femur and proximal tibia assessed by repeated measures using computer navigation system for total knee replacement, assessed intra-operatively (Group A).

2. Radiographic implant location, consisting of multi-parameter assessment of the relative position and orientation of the femoral and tibial components and overall limb alignment, assessed by the Perth CT protocol 3 months after surgery (Group B).

The secondary endpoint of this study is:

3. Knee function, quality of life and pain assessed 6 months after surgery (Group B).

The study objectives are:

1. Repeatability of the cutting guide position will be no worse than that obtained for manual instruments used for total knee replacement (Group A).

2. Participants will have higher knee function scores and increased quality of life as compared to pre-operative state and equal or better as compared to other surgical techniques using historical controls (Group B)

The objectives of the Extension Study are:

1. The primary objective is to determine the clinical and radiographic outcomes at 12 months, 2 years and 5 years post surgery, in patients receiving a Triathlon Custom Fit Knee featuring Stryker ShapeMatch.
2. The secondary objective is to determine the revision rate (yearly cumulative percent revision), device-related adverse events and reoperation rates.

RESEARCH OBJECTIVES

The use of patient-specific cutting guides for total knee joint replacement is being developed and introduced to clinical practice by a number of orthopaedic device companies. Each system differs in the way in which the cutting guides are designed, the material which they are made from, the alignment philosophy and the radiological information on which they are based (e.g. X-ray, CT, MRI).

The overall goal of this study is to assess the impact of a new surgical technique developed by Stryker on the functional outcome of participants undergoing primary total knee joint replacement.

The repeatability in placing the cutting guides relies on the reference points used in the design of the block, and the ability of the surgeon to position it on the diseased joint surfaces of the knee without the availability of traditional alignment jigs (femoral intra-medullary rod, tibial extra- or intra-medullary alignment guide). Hence, the first objective of this study is to quantify the reproducibility of this new technique by assessing cutting guide position using a repeated-measures methodology. The results will be described as a standard error of measurement.

Early reports indicate that improved post-operative functional outcomes may result from the use of this new technology when used in combination with particular designs of total knee joint prosthetic components (Howell et al, 2008; Spencer et al, 2009). The second objective is to assess and quantify such changes in the short-term (6

months) post-operative period. Potential benefits may be seen in the general quality of life experienced by participants, reduced pain levels, and specific improvements in activities of daily living affected by knee function. Other parameters related to the procedure, such as operating time, blood loss and length of stay in hospital will also be assessed to determine if perceived benefits with the use of this new surgical technique can be realised in routine clinical practice. Comparison of the study findings will be made to published literature on the clinical outcomes of total knee replacement (e.g. Kolisek et al, 2007; Matziolis et al, 2007; Harwin et al, 2008).

In addition, a cadaver study is being planned to further explore the precision analysis including quantification of intra- and inter-observer variation in placement of the cutting guides. Subsequent clinical studies such as randomised, controlled trials (RCTs) are envisaged to provide higher levels of evidence. The results of the case series outlined in this proposal will allow future studies to be designed in a sound manner, ensuring patient numbers and study design are sufficient to provide statistically-significant outcomes.

4.0 NUMBER OF PARTICIPANTS

Group A: Six investigators will recruit a minimum of 5 cases per investigator and a maximum of 60 cases in total.

Group B: Four hospitals and five investigators will recruit a total of 100 cases.

Extension Study: Participants from Group B will be invited; a maximum of 100 cases will be included.

5.0 LENGTH OF STUDY AND PATIENT PARTICIPATION

The enrolment period for Group A is expected to be 3 months or until the required sample size is reached. For Group B, individual study participants will be seen for at least 6 months after surgery. The enrolment period is expected to be 6 months. Therefore it is anticipated that the entire study will take approximately 1.5 years to complete.

At the completion of the 6 month follow-up visit patients will receive an invite to continue participation in the study via enrollment into the Extension Study. Patients

will be required to give informed consent and will need to meet the Extension study inclusion and exclusion criteria (see sections 6.3 and 6.4).

6.0 PATIENT SELECTION CRITERIA

Each Investigator is responsible for evaluating each patient against the following criteria and assuring that the patient meets the requirements to be enrolled in this clinical investigation. Each patient enrolled in this investigation must meet each of the following inclusion criteria and have none of the exclusion criteria. Any patient enrolled in this study who does not meet the inclusion and exclusion criteria will be considered a protocol deviation.

6.1 Inclusion Criteria

- The patient is a male or non-pregnant female between the ages of 50-90.
- The patient requires a primary total knee replacement and is indicated for computer-assisted surgery.
- The patient has a primary diagnosis of osteoarthritis (OA).
- The patient has intact collateral ligaments.
- The patient is able to undergo MRI scanning of the affected limb.
- The patient has signed the study specific, HREC-approved, Informed Consent document.
- The patient is willing and able to comply with the specified pre-operative and post-operative clinical and radiographic evaluations.

6.2 Exclusion Criteria

- The patient has a history of total, unicompartmental reconstruction or fusion of the affected joint.
- Patient has had a high tibial osteotomy or femoral osteotomy.
- The patient is morbidly obese (BMI ≥ 40).
- The patient has a deformity which will require the use of stems, wedges or augments in conjunction with the Triathlon Total Knee System.
- The patient has a varus/valgus malalignment ≥ 15° (relative to mechanical axis).
- The patient has a fixed flexion deformity ≥ 15°.

- The patient has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device.
- The patient has a systemic or metabolic disorder leading to progressive bone deterioration.
- The patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements.
- Patient has a cognitive impairment, an intellectual disability or a mental illness.
- The patient is pregnant.
- The patient has metal hardware present in the region of the hip, knee or ankle (as this is known to create geometrical distortion in the region of the implant).
- The patient has any known contraindications for undergoing assessment by MRI (e.g. ferrous implants, metallic clips, magnetically activated implanted devices such as cardiac pacemakers, etc).

6.3 Extension Study: Inclusion Criteria (applicable to patients electing to continue participation in the Extension study).

- Patient was enrolled in TriShapeMatch-10 study and completed 3 month follow-up visit.
- Patient is willing and able to give informed consent to participate in the study.
- Patient is willing and able to comply with the specified clinical and radiographic evaluations.

6.4 Extension Study: Exclusion Criteria (applicable to patients electing to continue participation in the Extension study).

- Patient no longer has the Triathlon Custom Fit Knee featuring Stryker ShapeMatch *in situ*, including patients that have had revision surgery.
- Patient has a cognitive impairment, an intellectual disability or a mental illness.
- Patient no longer resides in a geographical location that would reasonably permit clinic visits at protocol specified intervals.

7.0 STUDY DESIGN

Group A: This is a repeatability study of ShapeMatch® patient-specific cutting guides designed for participants undergoing total knee arthroplasty with the Triathlon® Total

Knee System (Stryker Orthopaedics, Mahwah NJ, USA) and Stryker eNact Knee Navigation System (Stryker Navigation, Kalamazoo MI, USA). Participants will undergo pre-operative assessment using MRI of the affected limb according to the scan protocol (see Appendix 2 for example). At the time of surgery, a repeated-measures methodology will be implemented in which the position of the femoral and tibial cutting guides will be measured using the Navigation system. The same surgeon will position each cutting guide a total of 3 times for each patient. Multiple participants will be assessed by each surgeon. No bone resections will take place using the patient-specific cutting guides. After the study-specific measurements have been taken, the total knee procedure will resume using the Navigation system and associated instruments being used to prepare the distal femur and tibia prior to implantation of the Triathlon® total knee components. No post-operative evaluations will be undertaken as part of this sub-study. However, participants will have routine visits, as per the investigators' standard-of-care for such participants.

Approximately30 participants (5 per investigator) up to a maximum of 60 participants will contribute to this sub-study.

Group B: This is a consecutive sample survey of participants undergoing total knee arthroplasty with the Triathlon® Total Knee System (Stryker Orthopaedics, Mahwah, NJ USA) utilizing ShapeMatch® patient-specific cutting guides to prepare the bony resections on the distal femur and proximal tibia. Health status and functional outcome measures will be recorded to quantify functional status of subjects before surgery and at each follow-up interval.

Participants suitable for primary total knee arthroplasty and indicated for computer-assisted surgery will be booked for surgery. Recruitment will be subject to gaining suitable informed consent from the patient.

Participants will undergo pre-operative assessment using MRI of the affected limb according to the scan protocol (Appendix 2).

Appropriate total knee replacement components from the Stryker Triathlon® Total Knee System will be used.

All patients undergoing total knee replacement routinely have anterior-posterior (AP) and medio-lateral (ML) X-rays taken of the affected knee pre-operatively and post-operatively. In addition, a more comprehensive assessment of total knee replacement component position and orientation will be obtained using the Perth CT protocol (Appendix 3; Chauhan et al, 2004).

Demographic details, diagnosis, coexistent disease and concomitant medications will be collected preoperatively and adverse events will be collected during and after surgery. Surgeons will monitor participants following surgery as per their standard of care for such participants.

Participants will follow the standard postoperative rehabilitation program established by the investigator at the study site.

Subjects

Subjects will be screened using the inclusion and exclusion criteria, and enrolled from the clinic after informed consent has been obtained. Their personal information and co-morbidities will be recorded from the chart and functional status will be assessed using the International Knee Society Score, SF-12 v2, Knee Osteoarthritis Outcome Score (KOOS), and Pain Visual Analog Scale. All information will be kept strictly confidential.

Demographic details and body mass index will be collected preoperatively and complications will be collected after surgery.

8.0 DEVICE DESCRIPTION

8.1 Device Trade Name

The instruments used to resect the distal femur and proximal tibia as part of this study will be referred to as the **Stryker ShapeMatch® Cutting Guides**. These devices are single-use, patient-specific instruments, approved for use in Australia by the Therapeutic Goods Administration.

The prosthetic components to be implanted as part of this study will collectively be referred to as the **Stryker Triathlon Primary Total Knee System**. Within this system, various individual implants of different designs, sizes and thicknesses are included, including:

- CR Femoral Component – Cemented
- CR Femoral Cementless Component – Beaded with Peri-Apatite
- PS Femoral Component – Cemented
- PS Femoral Cementless Component – Beaded with Peri-Apatite
- Primary Tibial Baseplate – Cemented
- Primary Tibial Baseplate – Beaded with Peri-Apatite
- CR Tibial Insert – X3
- CS Tibial Insert – X3
- PS Tibial Insert – X3

The **Stryker Triathlon Primary Total Knee System** is a commercially available, TGA (Therapeutic Goods Administration) listed device, and has been approved for sale and use throughout Australia.

In addition, the **Stryker eNact Knee Navigation System**, comprising of computer hardware and software and associated instrumentation, will be used for intra-operative assessment of implant and limb position. This system is a commercially available, TGA (Therapeutic Goods Administration) listed device, and has been approved for sale and use throughout Australia.

8.2 Device Supply

The Triathlon Primary Total Knee System, ShapeMatch® Cutting Guides and eNact Knee Navigation System will be supplied by Stryker Australia Pty Ltd.

9.0 SURGICAL PROCEDURES

Group A:

Each patient will be prepared to undergo a primary total knee replacement using the Triathlon Primary Total Knee System and Stryker eNact Knee Navigation System. A standard skin incision and joint exposure will be performed according to the surgeon's

preference. Navigation trackers will be secured to the femur and tibia and registration of the limb will be undertaken according to the surgical technique.

The appropriate Stryker ShapeMatch® Cutting Guide will be positioned onto the distal femur. A Navigation tracker with Resection Plane Probe attached will be placed into the cutting slot of the cutting guide. The location (position and orientation) of the probe is displayed on the computer screen of the Navigation system. The screen will be diverted from the surgeon's view and a recording will be made of the position once the surgeon has indicated that the cutting guide is positioned appropriately. The cutting guide will then be removed from the femur, and the process repeated until a total of three measurements have been recorded. The same procedure will be performed on the proximal tibia using the appropriate Stryker ShapeMatch® Cutting Guide. This entire process should take no longer than 5 minutes.

Once these measurements have been performed, the surgeon will resume the surgical technique for implantation of the Stryker Triathlon Primary Total Knee System using Stryker eNact Knee Navigation System, as per their own instrument and implant preferences.

Appropriate post-operative care will be provided according to the preference of the treating physician. No further evaluations will be required by study participants.

Group B:

Each patient will be prepared to undergo a primary total knee replacement using the Triathlon Primary Total Knee System and Stryker eNact Knee Navigation System. A standard skin incision and joint exposure will be performed according to the surgeon's preference. Navigation trackers will be secured to the femur and tibia and registration of the limb will be undertaken according to the surgical technique.

The appropriate Stryker ShapeMatch® Cutting Guide will be positioned onto the distal femur, and secured in place using fixation pins. A Navigation tracker with Resection Plane Probe attached will be placed into the cutting slot of the cutting guide. The location (position and orientation) of the probe will be displayed on the computer screen of the Navigation system and stored for future reference. The distal femoral

bone resection will be completed and the block removed. Completion of the bone preparation of the distal femur will be undertaken using manual instruments.

The same procedure will be performed on the proximal tibia using the appropriate Stryker ShapeMatch® Cutting Guide.

Trial components will be inserted into the joint and measurements of limb alignment and joint kinematics will be performed using the Navigation system.

Each of these measurements form routine assessments performed during total knee replacement surgery using the Stryker eNact Navigation System.

Once these measurements have been performed, the surgeon will resume the surgical technique for implantation of the Stryker Triathlon Primary Total Knee System using either CR or CS components. If the surgeon identifies intra-operatively that treatment using PS components is deemed more suitable, then this will be carried out. The final choice of components used will be noted on the relevant Case Report Form.

Appropriate post-operative care will be provided according to the preference of the treating physician. Post-operative assessments will be undertaken according to the study protocol.

10.0 INFORMED CONSENT

The Investigator will inform potential study candidates of the purpose of the study, proposed duration of the study, including the study-specific procedures and evaluations. The Investigator will discuss foreseeable risks involved, as well as potential benefits that may result for future participants through the outcomes of this study. Following this verbal discussion with the Investigator, participants will then be given time to read, understand, and, if agreeable, sign the study-specific Participant Consent Form indicating their agreement to participate in the study.

De-identified patient information will be used during the analysis of the results of the clinical study and the confidentiality of the participants will be maintained at all times. Patient records will be stored with the surgeon's normal secure record storage system.

The participants will be informed by the Investigator that they are free to refuse participation in this Investigation, and if they decline or withdraw from the study at any time this will not compromise further medical care.

A signed and dated Participant Consent must be obtained by the Investigator from the patient prior to enrolment into this study. The original signed and dated information sheet and patient consent will be kept by the Investigator. A copy will be provided to the patient, and another copy placed in the patient's hospital medical record.

Should a patient undergo any study procedure without signing a Participant Information and Consent Form, the Investigator must notify the applicable Ethics Committee and study sponsor of the deviation, detailing the circumstances which resulted in the failure to obtain informed consent. The Investigator will then follow Ethics Committee instructions on how to handle patient/situation and obtaining consent.

Patients willing to participate in the extension study will undergo a second consent process with a new patient information sheet detailing the additional study-specific procedures. This process will be carried out in the same manner as the original consent.

11.0 EVALUATIONS

All data will be recorded on the Case Report Forms. The designated signatory (e.g. investigator, delegated authority, participant, etc) will complete and sign forms at the time of each required visit specified by the study protocol.

Only participants in Group B will have detailed information collected pre- and post-operatively as part of their involvement in this study. Participants will have Anterior-

Posterior (AP) and Medio-Lateral (ML) X-rays taken pre-operatively and post-operatively as part of their standard-of-care. In addition, a CT scan according to the Perth CT protocol will be taken post-operatively. Participants will be assessed at 6 weeks, 3 months and 6 months after surgery.

The following data will be captured throughout the study:

Patient Demographics (Groups A & B): A record of the patient's date of birth, gender, height, weight, and medical history will be obtained pre-operatively.

Operative Details (Groups A & B): A summary of the surgical procedure will be collected during the operation. This will include details of the surgical approach, prosthetic components implanted, operating time and comments. In addition, measurements will be taken intra-operatively using the Stryker eNact Knee Navigation System. This will quantify cutting guide position, limb alignment and limb kinematics during the procedure.

Medical Imaging (Group B and Extension Study participants only)
Standard AP and ML X-rays of the affected limb will be obtained pre-operatively and post-operatively. A CT scan according to the Perth CT protocol (Appendix 3; Chauhan et al, 2004) will also be undertaken to obtain detailed three-dimensional descriptions of the position and orientation of the implant components. This position will be compared to the pre-operative plan to assess the efficacy of the customized bone cutting guides to implement the alignment goal.

In the Extension Study, participants will undergo two Long Leg AP weight bearing x-rays to evaluate alignment of the limb; one at 12 months and one at 5 years post surgery.

Patient outcome measurements (Group B only)

The International Knee Society System (IKSS) separates findings in the operated knee with findings in the patient's function. As such the Knee Score is not artificially affected by co-morbid conditions. The Knee Score consists of points given for pain, range of motion, and stability in both the coronal and sagittal planes, with deductions

for fixed deformity, and extensor lag. The Function Score consists of points given for the ability to walk on level surfaces, and the ability to ascend and descend stairs, with deductions for the use of external supporting devices (Appendix 4; Insall et al; 1990).

SF-12 v2: is a multi-purpose, short-form health survey with only 12 questions, derived from the original SF-36. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (Appendix 4; Ware, 2000). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-12 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

KOOS: Self administrating survey form which assesses the patient's opinion about their knee and associated problems. It is designed to assess subjects with relatively high-level of knee joint function and hence can be used to minimize ceiling effects resulting from other less-discriminating knee outcome scores. It consists of 5 subscales: pain; symptoms; function in daily living; function in sport and recreation and knee-related quality of life (Appendix 4; Roos et al; 1998). The original and complete WOMAC Osteoarthritis Index (more typically used for assessment of osteoarthritic knee function) is also contained within KOOS, and can be calculated as a sub-scale.

VAS: A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain. From the patient's perspective this spectrum appears continuous - their pain does not take discrete jumps, as a categorization of none, mild, moderate and severe (Wewers et al, 1990).

FJS-12: The Forgotten Joint Score is a newly-developed twelve-item, self-reported assessment of how aware recipients of hip and knee joint replacement are of their joint in everyday life (Behrend et al, 2012).

Medical History Review: For participants in the extension study, details of any significant medical events from time of surgery to 12 month visit will be recorded to ensure no adverse events have occurred between termination from Group B study and re-enrolment into Extension study.

All information on general medical, operative and device related complications will be documented and tabulated on case report forms (CRF).

All information on complications (date of occurrence, description, severity, related to study device, treatment and resolution) will be recorded at the time of occurrence.

All information on protocol deviations including the type of deviation (informed consent, inclusion/exclusion criteria, treatment, tests not performed and follow-up) will be recorded at the time of occurrence.

12.0 STATISTICAL METHODS

12.1 Sample Size Justification

Group A

No published data currently exists on the reliability and repeatability of the ability of surgeons to position the patient-specific cutting guides on the femoral and tibial bone surfaces. This is an observational case series with no sample size calculation. The study uses a sample size of convenience, based on the number of study sites and anticipated recruitment rate at each site.

Group B

Howell et al (2008) reported improvements in post-operative Knee Society Score resulting from the use of ShapeMatch® Cutting Guides for total knee replacement. A comparison of these results with those reported by Matziolis et al (2007) when using computer-assisted surgery for total knee replacement suggests that such differences may be clinically significant. An improvement of 15 points in the Knee Society Score (from 150 to 165 points, out of a maximum of 200) with a standard deviation of 35 can be assumed as representing a clinical significant improvement. Using these figures,

with 80% power, power analysis indicates that 87 patients per group are required. This does assume comparison of two independent groups with the t-test. Allowing for patient drop out, a minimum of 100 cases is recommended.

All 100 cases will be invited to participate in the Extension Study.

12.2 Data Capture and Analysis

All data will be recorded on 2-part NCR paper Case Report Forms (CRFs). The surgeon will complete and sign forms at the time of completion. Original CRFs will be collected by Stryker for data entry. Copies will remain at the investigator site. Archiving will be undertaken in accordance with ICH/GCP guidelines (Appendix 6).

Any unclear or ambiguous data will be queried and all cleaned data will be entered into a database for tracing purposes.
The primary outcome data gathered from Group A will be assessed using a repeated-measures analysis (Hopkins, 2009) to determine the mean and standard error of measurement between successive pairs of trials. Multiple surgeons gathering repeated measures on individual patients will be pooled to take into account varying knee anatomies and intra-observer variation.

The data from Group B and the Extension Study will be summarised and descriptive statistics will be utilised for analysis of the primary and secondary outcomes. The mean, median, standard deviation, minimum and maximum will be presented for quantitative variables. Statistical tests will be employed as deemed appropriate by a biostatistician. A significance level of 0.05 will be used for comparative tests.

Adverse events will be tabulated separately and reviewed for any commonalities. Revision surgery data from the Extension Study will be compared to the revision rates reported in the National Joint registry Report at 12 months, 2 years and 5 years. A cost benefit analysis will be undertaken with the use of data from the Australian Government Hospital Casemix Protocol Annual Report.

A formal interim analysis will take place following completion of each Group A and Group B sub-studies. Additionally, formal interim analyses will take place following all

participants' completion of the 12 month visit, again following completion of all participants' 2 year visit and final analysis will take place following completion of all participants' 5 year follow-up visits.

13.0 SELECTION CRITERIA FOR INVESTIGATORS/SITES

- The Investigator/s selected to participate in this study is/are qualified Orthopaedic surgeon/s.
- Research assistants and study staff will be representatives of the Institute under the direction of the Principal Investigator.
- Any conflicts of interest (including financial assistance from other parties) will be declared by investigators and research personnel before the commencement of the trial.
- Investigators must maintain a list of any delegated duties with respect to the trial, and the persons and qualifications of those persons to whom the duties are assigned.
- Sites must be able to demonstrate that adequate subject recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff.
- Investigators must provide medical care to a trial participant that is necessary as a result of any adverse event experienced during or following the trial that is deemed related to the trial.
- Investigators must possess, prior to trial commencement, a favorable Human Research Ethics Committee (HREC) endorsement of trial protocol, patient information and consent forms and any other information given to subjects.
- All trial related documents are subject to HREC review. A regular trial report is also mandatory for provision to the HREC (in accordance with local HREC requirements).
- The investigator/institution shall permit trial related monitoring, audits, HREC review and regulatory inspections, by providing direct access to source data/documents and any other trial related documentation.
- The trial MUST be conducted according to the approved protocol.
- Any deviation from the protocol must be documented for later review.

- No deviation from protocol may occur without HREC endorsement, unless it is required to prevent imminent harm to participants
- Investigators must ensure subjects have given informed, written consent, with all trial procedures and risks adequately explained.

14.0 ADMITTANCE OF PATIENT

The Investigator must wait for written Ethics Committee and Governance approval prior to beginning the study or enrolling participants.

A review of the inclusion and exclusion criteria must be completed by the Investigator pre-operatively for each patient.

A patient will be identified as a patient in this clinical trial upon signing a study informed patient consent form.

15.0 PATIENT ACCOUNTING

The investigator or designee will complete an informed consent log with details (patient number and initials) of any patient signing a consent form to participate in this study.

Clinical trial data will be monitored regularly to identify any trends and adverse events. Documentation of participants who voluntarily withdraw from the study or who are lost to follow-up will be obtained on a Study Completion Form.

16.0 QUALITY ASSURANCE OF DATA

Case Report Forms will be routinely reviewed by the Principal Investigator for completeness and accuracy as well as any evidence which may be indicative of patient risk. When any discrepancies are noted, they will be resolved with the Investigator and/or individual designated by the Investigator. When the data are incomplete, attempts will be made to obtain the data whenever possible.

Stryker Australia will monitor each investigational site at regular intervals to ensure compliance with the protocol and capture of any data or complications not already

documented. Verification of the data from source documents will also be conducted by the Stryker monitors.

17.0 MANAGEMENT OF CONCURRENT EVENTS

17.1 Concurrent illness/procedures

Participants requiring concurrent procedures or medications for inter-current illnesses or adverse events will not be restricted throughout the study. Given the typical patient population receiving total knee joint replacements, it can reasonably be expected that concurrent illnesses or procedures may be experienced by study participants.

17.2 Withdrawal from Study

Participants will be advised that they may voluntarily withdraw from the study at anytime, for any reason and they are not obligated to reveal the reason to the Investigator and it will not affect their medical care. However, in such cases, appropriate effort will be made to determine the reason for withdrawal from the study. The Investigator may request a letter from the patient noting his or her desire to withdraw from the study. All attempts to locate participants lost to follow up will also be documented.

Participants will be informed that should they withdraw from the study they should remain under the care of an appropriately experienced physician until the physician deems further follow-up unnecessary.

The following are circumstances for which a patient would be identified as not continuing their participation in the study:

- Study Completed / Terminated
- Death
- Unable to Return
- Unwilling to Return
- Concurrent Illness
- Lost to follow-up

- Re-operation of the affected knee joint, including revision of total knee replacement components
- Other

Additionally, the patient may be withdrawn by the Investigator, if he/she is unable to continue participation in the study due to some condition unrelated to this study.

A Study Completion Form will be completed for all participants who withdraw from the study.

18.0 MODIFICATION OF PROTOCOL

No changes to this Protocol will be permitted without the written approval of the applicable Ethics Committee.

Protocol deviation details should be recorded on a Protocol Deviation Form as soon as identified and notification will be made to the applicable Ethics Committee according to the Ethics Committee requirements.

19.0 DEFINITIONS AND REPORTING OF ADVERSE EVENTS

19.1 Definitions

Adverse Events:
Any undesirable clinical occurrence in a subject, whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Expected: An adverse event is expected when the specificity and severity of the event is consistent with a complication that is not related to the device but may be related to the surgical procedure.

Unexpected: An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the standard. It refers to an adverse event that has not been observed before.

Adverse Device Event

A clinical sign, symptom or condition that is causally related to the product, implantation procedure, the presence of product or the performance of the device system.

Serious Adverse Advent (SAE):

Any untoward medical occurrence that:

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or;
- Is a medically important event or reaction.

19.2 Reporting of Events

Adverse Events:

Any adverse event that occurs at any time point from the beginning of the surgical procedure until either the patient is terminated from the study, or 30 days post-completion, should be recorded as follows:

All information on general medical, operative and device related complications (adverse events) will be documented on case report forms (CRFs). Information should include date of occurrence, description, severity, relationship to study device, treatment and date of resolution.

The investigator must determine if the event is related to the device. Any adverse event in a study patient must be monitored until the event is resolved or considered non-clinically significant by the Investigator.

Expected Events: Should be reported to the sponsor soon as possible, but not later than ten working days after the Investigator first learns of the effect.

Adverse Device Events

Should any adverse device events occur, the study staff will ensure that these are documented by the Investigator and reported immediately to the Sponsor. They should also be reported to the reviewing Ethics Committee and Institution as soon as possible, but not later than fifteen working days after the Investigator first learns of the effect, unless an earlier timeline is specified by individual study sites. The Investigator with the Sponsor will conduct an evaluation of such effects. Following this evaluation, if the Investigator determines that an unanticipated adverse device effect presents an unreasonable risk to participants, the Investigation will be terminated as soon as possible. Termination shall occur no later than five working days after the Investigator makes this determination and no later than fifteen working days after the Investigator first receives notice of the unanticipated adverse effect.

Serious Adverse Events:

Any adverse event that is considered to be of serious nature and occurs at any time point from the signing of Informed Consent Form until either the patient is terminated from the study, or 30 days post-completion, should be recorded as follows:

All serious adverse events (SAEs) should be reported immediately to the sponsor by email or fax, **no later than 24 hours** after becoming aware of the event. The immediate reports should be followed promptly by detailed, written reports. Reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse device reactions to the regulatory authority (TGA) and the ethics

committee. All other Serious Adverse Events that are NOT related to the device will be reported to the ethics committee in a table with the annual reports, or as otherwise directed by the relevant ethics committee.

20.0 HUMAN RESEARCH ETHICS COMMITTEE (HREC)

20.1 Approval

The Investigator is responsible for obtaining Ethics Committee and Governance approval to conduct this study.

20.2 Prior to Initiation of the Study

The Investigator must wait for written approval by their Ethics Committee and Governance Officer prior to beginning the study. The Investigator may discuss the study with prospective participants; however, the Investigator may not obtain written Patient Informed Consent, nor perform study procedures on prospective study participants, until all required approvals are granted.

20.3 Progress Reports

The Investigator will also submit, at intervals requested by the Ethics Committee, progress reports on this study. These progress reports will be submitted to the sponsor and to the Investigator's Ethics Committee.

20.4 Withdrawal of Ethics Approval

Should the Ethics Committee withdraw its approval, the Investigator will notify the Sponsor no later than five working days following such withdrawal.

20.5 Final Reports

Upon completion of the Investigation, each Investigator will submit an Ethics Close-Out Report on his/her part of the Investigation within three months of completion of the Investigation. This report will be submitted both to the Sponsor and the Investigator's Ethics Committee.

21.0 SPONSOR RESPONSIBILITES

21.1 Reports

The Sponsor, upon completion of the study, will prepare a comprehensive Final Report. These reports will be submitted to the Investigator/s, and ethics committee/s. Any significant results from interim analyses will be communicated to the Investigator/s and ethics committee/s, and any required changes to the protocol as a result of these analyses will be submitted as protocol amendments to the reviewing HREC.

21.2 Clinical Monitoring of the Study

The Sponsor will monitor and ensure that this study is conducted in accordance with the signed investigator Clinical Trial Agreement, The Protocol, conditions imposed by the Ethics Committee, as well as other applicable regulations. Prior to initiating any study related activities, the Sponsor will conduct an appropriate pre-investigational visit and further communication to ascertain that:

- The investigator/s understand and accept his/her obligation in conducting the study
- The investigator/s understand the use of the device
- The investigator/s and staff have sufficient time and access to the adequate number of subjects required for the study
- The investigator/s understand that the study does not begin until written approval of the protocol is obtained from the ethics committee and all conditions of the ethics committee approval have been met
- The investigator/s and study staff understand and can complete the required case report forms
- The investigator/s have signed a Clinical Trial Agreement and have a current curriculum vitae on file
- The investigators ethics approval is on file.

During the course of the study, the clinical monitors conduct periodic visits at intervals and maintain regular contact with the Investigator/s and his/her staff to ascertain completeness and accuracy of data being collected as well as any evidence which may be indicative of subject risk. When any discrepancies are noted in the data, they will be resolved with the Investigator/s or his/her designee. When data are incomplete, they will be obtained whenever possible.

The Monitor will report to the Stryker Clinical Research Manager any non-compliance by the Investigator with the signed Clinical Trial Agreement, the Protocol, the requirements of any TGA regulation, or any condition imposed by the reviewing ethics committee. The Sponsor will secure compliance from the Investigator or terminate the investigator's participation in the study. Ethics Committee approval will be obtained prior to resuming a terminated Study. Should any deviations from the Protocol occur, these will be reviewed by the monitor for their clinical significance and appropriately documented and reported.

22.0 USE OF INFORMATION AND PUBLICATIONS

Investigators must respect the confidentiality of data, especially regarding its use by potential competitors.

The information gathered during this study will be disseminated in journals and conferences. Anonymity of the participants involved in the study will be maintained at all times.

23.0 ANALYSIS/CONCLUSIONS

The data obtained in this Investigation will be maintained and periodically assessed throughout the study. Based on the above design and planned analysis, we believe this Case Series Protocol is scientifically sound and that the clinical evaluation of the experimental procedure is justified.

24.0 BIBLIOGRAPHY

1. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The "forgotten joint" as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome measure. J Arthroplasty. 2012 Mar;27(3):430-436.e1.

2. Bourne RB, Chesworth BM, Davis AM, et al. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res. 2010 Jan;468(1):57-63.

3. Chauhan SK, Clark GW, Lloyd S et al. Computer-assisted total knee replacement – A controlled cadaver study using a multi-parameter quantitative CT assessment of alignment (The Perth CT Protocol). JBJS (Br) 2004; 86-B:818-23.

4. Chauhan SK, Scott RG, Breidahl W. Computer-assisted knee Arthroplasty versus a conventional jig-based approach. JBJS (Br) 2004; 86-B:372-7.

5. Coughlin KM, Incavo SJ, Churchill DL et al. Tibial axis and patellar position relative to the femoral epicondylar axis during squatting. J Arthroplasty 2003; 18(8):1048-55.

6. Eckhoff DG, Bach JM, Spitzer VM et al. Three-dimensional mechanics, kinematics, and morphology of the knee viewed in virtual reality. JBJS (Am) 2005; 87-A:71-80.

7. Hopkins WG. A new view of statistics [online] http://www.sportsci.org/resource/stats/ Accessed 1/7/2010.

8. Harwin SF, Greene KA, Hitt K. Triathlon total knee arthroplasty – 4-year outcomes with a high-performance implant. J Knee Surg 2008; 21:320-6.

9. Howell SM, Kuznik K, Hull ML et al. Results of an initial experience with custom-fit positioning total knee Arthroplasty in a series of 48 participants. Orthopedics 2008; 31(9):857-63 [online] http://www.orthosupersite.com/view.asp?rID=31412 Accessed 23/9/2009.

10. Insall JN, Dorr LD, Scott RD et al. Rationale of the Knee Society clinical rating system. Clin Orthop 1989; 248:13.

11. Insall JN & Scott WN (eds). Surgery of the Knee- 3rd Edition. Churchill Livingstone, Philadelphia. 2001.

12. Kolisek FR, Bonutti PM, Hozack WJ et al. Clinical experience using a minimally invasive surgical approach for total knee arthroplasty. J Arthroplasty 2007; 22(1):8-13.

13. Matziolis G, Krocker D, Weiss U et al. A prospective, randomized study of computer-assisted and conventional total knee arthroplasty – Three-dimensional evaluation of implant alignment and rotation. JBJS (Am) 2007;89:236-43.

14. Roos EM, Roos PH, Lohmander LS et al: Knee injury and Osteoarthritis Outcome Score (KOOS): Development of a self-administered outcome measure. J Orthop Sports Phys Ther. 1998;78(2): 88-96.

15. Spencer BA, Mont MA, McGrath MS et al. Initial experience with custom-fit total knee replacement: intra-operative events and long-leg coronal alignment. Int Orthop 2009 33(6):1571-5.

16. Ware JE Jr. SF-36 health survey update. Spine 2000; 25(24):3130-9.

17. Wewers, M, Lowe N. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990; 13: 227-36.

APPENDIX 1

OtisMed Custom Fit Total Knee Replacement Using ShapeMatch® Technology

APPENDIX 2

MRI Scan Protocol

APPENDIX 3

CT Scan Protocol

APPENDIX 4

Outcome Assessment Tools

APPENDIX 5

Declaration of Helsinki

APPENDIX 6

ICH Good Clinical Practice (GCP) Guidelines